REMARKS

Claims 2 and 10 - 14 have been cancelled without prejudice, and claims 1, 4, 9 and 15 have been amended to more clearly state the invention. In addition, new claims 16 - 24 have been added. New claim 16 depends on claim 15, which relates to a method for detection of autoimmune antibodies. Claims 17 - 20 claim peptides derived from an antigen produced by mRNA encoding a filaggrin or profilaggrin antigen, comprising at least one arginine residue, wherein the peptide further comprises at least one modified arginine residue. Claims 21 - 24 claim specific peptides of this invention.

In response to the Detailed Action, Applicants state:

1. **Lack of Unity.** Applicants acknowledge the rejoinder of groups I, II and V as set forth in the Office Action.

2. **Withdrawal of Claims 10 - 14.** Applicants acknowledge that claims 10 - 14 are withdrawn by the Examiner as being drawn to a nonelected invention, and acknowledges the Examiner's comments regarding inventorship. Claims 10 to 14 are cancelled without prejudice.

3. **Abstract of the Disclosure.** Applicants note that under PCT and international practice the abstract was presented in the cover page of international application WO98/22503 as published. Applicants have amended the specification to include an abstract, which abstract is as originally filed in the international application and appearing on the cover page thereof.

4. **Order or Arrangement.** Applicants have amended the specification to insert headings in compliance with preferred United States practice. Applicants have also correct certain typographical errors and informalities, as set forth above.

5. **Amendment to Status.** Applicants have amended the status to refer to both the PCT and the Netherlands national application.

6. - 7. 35 U.S.C. § 112, first paragraph, rejection of Claims 1 - 3, 5 - 9 and 15 - Written Description. Applicants have amended claim 1 to more clearly state the invention. It is noted as a preliminary matter that even under the analysis of the Examiner, claim 6 is not subject to rejection on this ground. The cyclic peptide of claim 6 is specifically described, see Formula XI of Fig. 1, and use of this cyclic peptide is specifically disclosed, see page 9, line 31 and following. Thus Applicants clearly had possession, under any analysis, of both the peptides disclosed in Table 1 and the peptide of Formula XI of Fig. 1. Accordingly, neither claim 4 nor claim 6 is subject to this ground of rejection.

The issue with respect to the written requirement depends on a review of the entire application and the state of the art. The Examiner's statement in the first paragraph of page 4 of the Office Action, to the effect that the "skilled artisan cannot envision all the contemplated peptides that are derived from any antigen recognized by any autoantibodies...", simply misses the mark. What is claimed is not peptides derived from any antigen, but rather peptides derived from antigens wherein the antigen is coded by mRNA "comprising a codon for at least one arginine residue", further wherein the derived peptide comprises at least one modified arginine residue with a specific and specified side chain, and further wherein the peptide is reactive with autoimmune antibodies from a patient suffering from rheumatoid arthritis. The class or genus of peptides covered by this claim are obvious to a skilled artisan, and it is similarly obvious how a skilled artisan would go about routine and ordinary steps to arrive at the peptides.

To the extent that the Examiner suggests that the specific amino acid sequence of all peptides must be precisely derivable from the claim, Applicants take exception. It is clear that the skilled artisan can readily envisage the peptides encompassed in claim 1. All have a common structural attribute consisting of a modified arginine. All are derived from an antigen encoded by mRNA that is recognized by autoimmune antibodies in patients with rheumatoid arthritis. The mRNA further has a common structural attribute in that it includes a codon for at least one arginine residue.

Applicants further note that new claim 17 is drawn to, inter alia, a peptide "wherein the peptide is derived from a contiguous stretch of amino acid residues encoded by mRNA encoding a filaggrin or profilaggrin antigen, the mRNA comprising a codon for at least one arginine residue." It is submitted that this clearly satisfies the written description requirement.

Applicants have performed extensive research to arrive at the insight disclosed in the present invention. A skilled artisan is aware of the fact that, in principle, an epitope is recognized irrespective of the remainder of the molecule it is part of or linked to. Hence, there is no need for further structural information. Should the skilled artisan so desire, he or she will select the further part of the molecule to suit his/her needs, as is indeed well known in the art.

For the present invention, Applicants disclose a peptide derived from an antigen recognized by specified autoantibodies, said peptide having the specific feature that it contains a modified arginine residue as specified. It is clearly within the capabilities of a person skilled in the art to look at the amino acid sequence of an antigen recognized by autoantibodies from patients with rheumatoid arthritis (such as disclosed by Simon et al.) select a region comprising an arginine residue and obtain, for example by means of the well known Merrifield synthesis, a peptide containing the modified arginine reside, to arrive at a peptide reactive with said autoimmune antibodies.

The route which a skilled artisan follows is not relevant. For example, it would be possible to employ ordinary combinatorial peptide chemistry, synthesizing, for example, 10^6 different peptides containing a modified amino acid as disclosed, screen with antibodies derived from a person suffering from rheumatoid arthritis, and thereafter determining the sequence of the recognized peptides. Thus, the person skilled in the art may employ alternative routes to arrive at a functional peptide derived from the antigen recognized by autoantibodies from a patient with rheumatoid arthritis. Similarly, a person skilled in the art can easily select a peptide not belonging to the group of 10 peptides given by way of example (and being the best peptides the Applicants had knowledge of at the time of filing the application), knowing that

a modified arginine residue such as citrulline residue as discovered by Applicants is key, and "invent around" Applicant's invention. Thus Applicants' invention consists not of just the specified peptides, but rather encompasses that class of peptides characterized as described by Applicants.

8. 35 U.S.C. § 112, first paragraph, rejection of Claims 1 - 3, 5, 7- 9 and 15 - Enablement. As discussed above with respect to written description, this ground of rejection is respectfully traversed. Applicants further note that the amendments made to claim 1 are believed to overcome this ground of rejection.

Contrary to the Examiner's assertion, the specification disclosure is more than sufficient to enable one skilled in the art to practice the invention with peptides other than those disclosed, and without an undue amount of experimentation. There is very specific biochemical information. The peptide must be (1) reactive with autoimmune antibodies in a patient with rheumatoid arthritis. Page 1, lines 23 - 24; see assay methods on page 7. The peptide must correspond to a part of a mRNA molecule coding for an arginine residue, the part comprising a codon for an arginine residue. Page 1, lines 24 - 26. Determining amino acid sequences corresponding to an mRNA is well known in the art, and requires no citation. Further, the arginine residue in the peptide must be modified, and in a specified manner. All of the modifications, and not just citrulline, are art convention side chain modifications, well known to those of ordinary skill in the art.

It is submitted that the reference to Abaza et al. is, while literally correct, not applicable. A single amino acid difference may well effect monoclonal antibody binding, and Applicants take no issue with that teaching. However, teachings with respect to a monoclonal antibody are not pertinent. The issue is whether the peptide is reactive with autoimmune antibodies from a patient with rheumatoid arthritis; these antibodies are, by definition, polyclonal. That is, we are simply involved with endogenous IgG present in a patient with rheumatoid arthritis. A change in one amino acid may result in one cohort of those antibodies with a particular affinity recognizing the peptide less well, while another peptide will better recognize the

antigen. The teaching of Abaza et al. is simply inapplicable. Further, as is taught by Applicants (see for example page 7) the use of assays, such as ELISA, to ascertain the peptides which bind is well known in the art. It is clear that functional or identifying characteristics, such as reactivity or specificity, may properly be employed to describe an invention. Lockwood v. American Airlines, Inc., 107 F.3d 1565, 41 USPQ2d 1961 (Fed. Cir. 1997).

9.-10. 35 U.S.C. § 112, second paragraph, rejection of Claims 1-9 and 15 - Indefinite. The claims have been amended to overcome the rejection.

11.-12. 35 U.S.C. § 101, rejection of Claim 15 - No Steps. Claim 15 has been amended to overcome the rejection.

14.-14. Claims 1, 2, 3, 7, 8 and 15 rejected under 35 U.S.C. § 102(a) as anticipated by Schellekens et al. A certified copy of the priority document together with a certified translation thereof in compliance with 37 C.F.R. § 1.55 is submitted herewith, and is requested to be made of record. Netherlands application 1004539, with a filing date of 11-15-1996, is prior to the publication date of the cited reference.

15. Claims 1, 2, 3 and 8 rejected under 35 U.S.C. § 102(b) as anticipated by Simon et al. as evidenced by WO/99/35167. It is asserted that the claims as amended overcome this ground of rejection. Claim 1 is now drawn to peptides of a specific length, which are not disclosed or anticipated by Simon et al. Further, it is noted that WO/99/35167 has a priority date subsequent to that of Applicants, and cannot properly be applied. From page 1392 of Simon M. et al, last paragraph above the Acknowledgements, it is clear that the epitope(s) are not known. In the instant application Applicants disclose epitopes characterized in that they contain a modified arginine residue, for which reason the present invention is new over this publication by Simon et al. Applicants show that these epitopes are suitable for reliably establishing a diagnosis for rheumatoid arthritis.

In view of the above amendments and remarks, it is respectfully submitted that all grounds of rejection and objection have been avoided and/or traversed. It is believed that the case is now in condition for allowance and same is respectfully requested.

If any issues remain, or if the Examiner believes that prosecution of this application might be expedited by discussion of the issues, he is cordially invited to telephone the undersigned attorney for Applicants, collect, at the telephone number listed below.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached paper is captioned "**Version with Markings to Show Changes Made**."

A check for additional claim fees is attached. Also being filed herewith is a Petition for Extension of Time to June 30, 2001, with the appropriate fee. Authorization is given to charge payment of any additional fees required, or credit any overpayment, to Deposit Acct. 13-4213. A duplicate of this paper is enclosed for accounting purposes.

Respectfully submitted,

Dated: July 2, 2001

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Version with Markings to Show Changes Made

In the Specification:

On page 4, third line, delete the word "combinationary" and insert in lieu thereof --combinatorial--.

On page 4, line 23, delete the world "recombinatory" and insert in lieu thereof --combinatorial--.

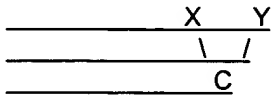
In the Claims:

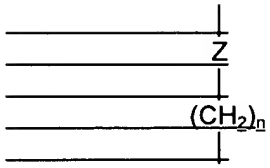
Please amend the claims as follows:

Cancel claims 2 and 10 - 14 without prejudice.

Amend the following claims:

1. (Twice Amended) A peptide of about 21 or fewer amino acids, [derived from an antigen recognized by autoantibodies from patients with rheumatoid arthritis, which peptide is] reactive with autoimmune antibodies from a patient suffering from rheumatoid arthritis, wherein the [derived] peptide [that is reactive with autoimmune antibodies] is derived from [corresponds to] a contiguous stretch of amino acid residues encoded by mRNA encoding an antigen recognized by autoimmune antibodies in a patient with rheumatoid arthritis, [part of a RNA molecule coding for the antigen,] said [part] mRNA comprising a codon for [an] at least one arginine residue, [and] wherein at least one [the] arginine residue in the [derived] peptide [, which is reactive with autoimmune antibodies, is a] comprises a modified arginine residue with a side chain of the formula:





wherein

X is NH_2, CH_3, $NHCH_3$ or $N(CH_3)_2$;

Y is O, NH, $NHCH_3$ or $N(CH_3)_2$;

Z is O, NH or CH_2; and

n is 2, 3 or 4, on the condition that when X = NH_3 and Z = NH, Y is not NH.

4. (Thrice Amended) A peptide according to claim 1 wherein the peptide comprises a linear peptide selected from the group of peptides consisting of SEQ ID NO 1, SFQ ID NO 2, SEQ ID NO 3, SEQ ID NO 4, SEQ ID NO 5, SEQ ID NO 6, SEQ ID NO 7, SEQ ID NO 8 [AND] and SEQ ID NO 9.

9. (Twice Amended) A peptide according to claim 1 wherein the peptide is obtained by the proteolytic treatment of (pro)filaggrin, separation of peptide fragments formed by proteolysis and subsequent selection of the presence of a modified arginine residue in a peptide, which modified arginine residue [which] was formed during the proteolytic treatment.

15. (Twice Amended) A method for the detection of autoimmune antibodies [wherein in an immunological test at least one immunologically reactive molecule selected from the group consisting of i) a peptide according to claim 1; ii) an organic compound according to claim 14; and iii) an antibody according to claim 10 is used] in sera of a patient, comprising the steps of:

contacting a peptide according to claim 1 with sera of the patient, and

detecting for the formation of a peptide and antibody complex.